NDA: 21-229
Product: Prilosec (omeprazole magnesium tablets 20.6 mg)
Sponsor: Astra Zeneca/Proctor & Gamble
Indication: Relief and prevention of heartburn
Marketing: OTC
Medical Reviewers: Ling Chin, M.D., M.P.H.
                     Daiva Shetty, M.D.

Introduction:

This is an application for Omeprazole-Magnesium MUPS tablets to be marketed Over-the-Counter (OTC). This is the first product in its class of proton pump inhibitors to be considered.

The clinical program conducted to support the labeling of omeprazole magnesium (Ome-Mg) for OTC use includes data generated from:
(1) 6 well-controlled clinical trials
(2) 5 actual use studies
(3) 1 label comprehension study and four additional at-home studies
(4) global post-marketing information

The pivotal efficacy and safety trials have been reviewed by the reviewers in the Division of Gastrointestinal and Coagulation Drug Products (HFD-180). This review will only focus on the studies pertaining to actual use of the drug under OTC conditions. The following studies are reviewed:
(1) Study 003
(2) Study 067
(3) Study 014
(4) Study 022
(5) Study 091

Global Post-marketing information for the following were also reviewed:
(1) Omeprazole magnesium MUPS tablet (European Rx experience, Swedish OTC experience)
(2) Omeprazole magnesium Delayed Release Tablets (Canadian RX experience)

The Final Monograph for Antacid Products issued in June of 1974 (39 FR 19874) allowed for an OTC indication for relief of heartburn for a specific list of antacid ingredients such as sodium bicarbonate. H_2 Receptor Antagonists (H2RAs) were approved for OTC treatment and prevention of occasional heartburn in 1995 and 1996. Thus the OTC treatment of heartburn with antacids and H2RAs is well established, and is intended for consumers with episodic (occasional) heartburn. In this application, a new product class (proton pump inhibitor) is being considered for OTC use for self-treatment and prevention of heartburn.

The sponsor has expanded the current heartburn indication for the OTC H2RAs from meal induced heartburn to heartburn from any precipitant. They have also expanded the acute treatment of heartburn and the immediate prevention of a meal-induced heartburn episode to prevention of heartburn anytime within a 24-hour time period.

Summary of Actual Use Studies:

Four out of five studies evaluated omeprazole-magnesium 20.6 mg-strength tablet and one (#022) the 10.3 mg-strength tablet. The primary objective of all five studies was to evaluate consumer usage pattern and dosing compliance. All five studies also evaluated the safety profile for the dosage studied. Subjective assessments of drug performance were obtained in

studies #003 and #067. Study #022 used a lower dose of omeprazole-magnesium (10.3 mg). Study #091 used a different formulation of omeprazole – 20 mg capsules. Study #014 and #091 were marketing studies where consumer usage patterns were also obtained.

Table 1. Overview of Actual Use Trials

	003	067	014	022	091
Design	Multi-center, multi-dose, open-label, at-home study				
Primary Objective	Usage pattern/ Dosing compliance	Usage pattern/ Dosing compliance	Usage pattern/ Dosing compliance (Marketing Study)	Usage pattern/ Dosing compliance	Usage pattern/ Dosing compliance/ Satisfaction (Marketing Study)
Secondary Objective	Effectiveness/safety	Effectiveness/safety	Only Safety	Effectiveness/safety	Safety/Satisfaction
Recruited/screened	1514	100	1516	923	374
Enrolled	1093	100	1440	596	368
ITT	825	92	939	489	352
Ages (mean)	13-84 (47)	12-17 (14)	18-82 (43)	13-87 (46)	18-77 (45)
REALM <60	84 (10%)	N/A	N/A	N/A	N/A
Centers (N)	7	2	61	5	12
Dose/Formulation	20.6 mg tablet	20.6 mg tablet	20.6 mg tablet	10.3 mg tablet	20 mg capsule
# tablets dispensed	36	36	12	36	20
Inclusion Criteria			HB for at least 1 mo and used HB meds for 1 mo		HB at least 2x/week and used HB meds at least 2x/week for 30d.
Exclusion Criteria					
Duration	4 weeks	4 weeks	4 weeks	4 weeks	3 weeks
Heartburn history	55% ≥5 years 63% ≥ 2-3 times/wk	85% >1 year 64% > 2-3 times/wk		45% > 5 years 59% > 2 times/week	
Usage pattern	Relief only: 38% Prevention: 10% Both: 52%	Relief only: 37% Prevention: 12% Both: 51%	Relief only: 26% Prevention: 19% Both: 52%	Relief only: 33% Prevention: 12% Both: 55%	Relief only: 22% Prevention: 16% Both: 62%
Overall consistency with 3 label direction	62%	75%	84%	58%	79%
>1 tablet per dose Overall	<15%	9%	4%	19%	6%
>1 tablet per dose Prevention	5%	9%	5%	21%	4%
>1 tablet per dose Relief	11%	3%	2%	10%	6%
# sequential dosing days Overall	<10 days 78% >10 days 22%	<10 days 74% >10 days 16%	<10 days 92% >10 days 8%	<10 days 78% >10 days 22%	<14 days 87% >14 days 13%
# sequential days Relief	<10 days 96% >10 days 4%	<10 days 100% >10 days 0%	<10 days 100% >10 days 0%	<10 days 97% >10 days 3%	<14 days 100% >14 days 0%
# sequential days Prevention	<10 days 35% >10 days 65%	<10 days 36% >10 days 64%	<10 days 70% >10 days 30%	<10 days 36% >10 days 64%	<14 days 51% >14 days 49%
Concurrent Meds	Antacids: 13% H2RAs: 2% PPIs: 1%	Antacids: 11% H2RAs: 8% PPIs: 0%	Antacids: 20% H2RAs: 19% PPIs: 3%	Antacids: 18% H2RAs: 2% PPIs: 3%	Antacids: ? H2RAs: ? PPIs: ?

None of these were all-comer studies. Each study imposed its own set of inclusion/exclusion criteria, which selected for individuals with no risk conditions for taking the drug, and/or had defined heartburn histories. All 5 studies evaluated consumer behavior with regard to the 3 labeled directions. None of the studies included an assessment of self-selection appropriateness. An assessment of whether consumers would seek physician consultation as labeled was not made in any of the 5 studies.

The overall consistency with all 3 labeled directions ranged from 58% to 84%. Study #014 had the best results but only 12 tablets were dispensed. All of the other studies dispensed 36 tablets except for #91 (20 tablets).

Subjects across all studies who used study drug for Prevention only consistently had a tendency to use the product for much a longer duration (# sequential days) than Relief only users.

Summary of Safety from Actual Use Studies:

Table 2. Overview of Safety from Actual Use Studies

	003	067	014	022	091
Design	Multi-center, multi-dose, open-label, at-home study				
Primary objective	Usage pattern/ Dosing compliance	Usage pattern/ Dosing compliance	Usage pattern/ Dosing compliance (Marketing objective)	Usage pattern/ Dosing compliance	Usage pattern/ Dosing compliance/ Satisfaction (Marketing objective)
Secondary objective	Effectiveness/safety	Effectiveness/safety	Only Safety	Effectiveness/safety	Safety/Satisfaction
Recruited/ Screened	1514	100	1516	923	374
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ITT	825	92	939	489	352
Ages (mean)	13-84 (47)	12-17 (14)	18-82 (43)	13-87 (46)	18-77 (45)
Dose/ Formulation	20.6 mg tablet	20.6 mg tablet	20.6 mg tablet	10.3 mg tablet	20 mg capsule
# tablets dispensed	36	36	12	36	20
# Exposed		92	939	489	352
# Dosing Occasions	10734	1-39	1-12	1-36	1-20
# AEs reported	292	94	532	210	81
# Reports	203	51	329	139	60
# Deaths	1 (not related)	0	0	1 (not related)	0
# SAEs	5	27	88	50	11
Top 4 Body Systems	Body as a Whole Digestive Respiratory	Body as a Whole Respiratory Digestive Cardiovascular	Body as a Whole Digestive Respiratory Nervous	Body as a Whole Digestive Respiratory Musculoskeletal	Digestive Body as a Whole Nervous Respiratory

Discussion:
Concerns about serious consequences arising from longstanding heartburn symptoms, (e.g. esophageal strictures, Barrett's esophagus), have been discussed in recent literature. While no definitive line has been drawn to separate episodic heartburn from the disease entity, gastroesophageal reflux disease (GERD) has been defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus (DeVault, Castell, ACG 1999)[1].

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[1] DeVault, Castell, et al. Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease. The Am J Gastroenterology 1999;94(6):1434-1442

The American College of Gastroenterology has described a distinction between occasional heartburn and heartburn that occurs with greater frequency. Heartburn that occurs more frequently than 2 times per week may be an indication of acid reflux disease, also known as GERD. When GERD is not treated, serious complications can occur, such as:
- severe chest pain that can mimic a heart attack
- esophageal stricture
- esophageal bleeding
- pre-malignant change in the lining of the esophagus (Barrett's esophagus)

Warning symptoms suggesting that serious damage to the esophagus may have already occurred include:
- difficulty swallowing (dysphagia) or feeling of food trapped behind sternum
- bleeding, vomiting blood, or black, tarry stools
- choking sensations, shortness of breath, coughing, or hoarseness of the voice
- weight loss
- chest pain

Patient information provided by the American College of Gasteroenterology[2] advised that a doctor should be seen if symptoms of heartburn are not controlled with lifestyle modifications, OTC medicines are needed more than 2 times a week, or symptoms remain unresolved.
The Updated Guidelines for the Diagnosis and Treatment of GERD,[1] published in 1999, also called for further diagnostic testing if warning symptoms are present.

The sponsor has stated that "episodic treatment of heartburn is different from the treatment of gastroesophageal reflux disease (GERD). In this application, however, the proposed indication is for prevention anytime within a 24-hour period. This, in essence, has changed the nature of using a drug product for episode-linked prevention to prevention of any number of episodes of heartburn within a set time period.

Conclusions:
There were several studies conducted to assess use of this drug under OTC conditions. Approximately 3500 subjects were enrolled into the 5 studies. The conclusions from these studies are limited to the following:

1. Overall consistency of subjects with dosing directions was <80% (except Study #014 which had fewer tablets dispensed).
2. Relief only users were more compliant with the dosing directions than the prevention only users.
3. Overall consistency by dosing occasions were much higher, i.e. each non-compliant subject is not non-compliant all of the time.
4. The majority of subjects took 1 tablet per dosing occasion and per dosing day.
5. Relief only users were more compliant with the dosing day restriction.
6. The majority of Prevention only users exceeded the 10-day use limit.
7. Correctness of subjects' self-selection decision was not assessed.
8. Performance of subjects with respect to certain risk conditions cannot be assessed:
    - pregnancy
    - difficulty swallowing
    - persistent stomach pains (>10 days)

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[2] - Patient Information from the Am College of Gastroenterology. www.acg.gi.org/acg-dev/patientinfo/
 - Gastroesophageal Reflux Disease (Hiatal Hernia and Heartburn). National Institute of Diabetes and Digestive and Kidney Diseases. www.niddk.nih.gov/health/digest/pubs/heartburn/heartbrn.htm

-   use of concomitant drugs.
9. Performance of subjects with respect to contacting a doctor or health care professional cannot be assessed.
10. Safety profile is unremarkable.

The subjects in these studies had to meet several inclusion/exclusion criteria before they could be enrolled, and may not be representative of the general OTC population who would use this drug once it is available OTC. Several questions about whether or not this product can be used appropriately OTC remain unanswered. What is clear is that there may be a difference between subjects using the drug for prevention only versus relief only purposes. The 10-day limitation on the product label is ineffective among the group of Prevention only users as 65% of this group used the study drug for over 10 days.

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